



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No.: 99-0903

June 2, 2000

Robert L. Garnick, Ph.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

Your biologics license application for Tenecteplase is approved effective this date. Genentech, Inc., South San Francisco, California, is hereby authorized to introduce or deliver for introduction into interstate commerce Tenecteplase under Department of Health and Human Services U. S. License No. 1048.

Tenecteplase is indicated for reduction of mortality associated with acute myocardial infarction (AMI). Under this authorization, you are approved to manufacture Tenecteplase drug substance and drug product, including filling and packaging, at your facility in South San Francisco, California. In accordance with approved labeling, your product will bear the tradename TNKase, and will be marketed in a 50 mg vial supplied with one 10 ml vial of Sterile Water for Injection, USP, one 10 ml syringe with TwinPak™ Dual Cannula Device, and three alcohol prep pads.

The dating period for this product shall be 36 months from the date of manufacture when stored at controlled room temperature not to exceed 30°C (86°F) or under refrigeration 2-8°C (36-46°). The date of manufacture shall be defined as the date of final sterile filtration of the formulated product. The dating period for the formulated final bulk shall be 24 months when stored at -20°C or 25 days when stored at 2-8°C. The expiration date for the packaged product shall be dependent on the shortest expiration date of any supplied component. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Tenecteplase to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). As communicated in our letter of February 15, 2000, a waiver for pediatric studies for this application is granted under 21 CFR 601.27.

We acknowledge your commitments to provide additional information and to conduct post-marketing studies as described in your letters of February 7, March 10, April 4, April 13, May 5, May 21, and May 30, 2000. As outlined below, you have agreed to:

1. Gather data from the National Registry of Myocardial Infarction (NRFMI) for a prospective registry study on U.S. patients presenting with acute myocardial infarction who are treated with TNKase™. The patient population will include 3,000 patients of African descent, 1,500 patients of Hispanic descent, 3,500 patients of low body weight (<60 kg) and a control group of >50,000 patients. The registry data will include information regarding demographics, past medical history, concomitant medications, treatment regimen, clinical outcome and patient disposition. Information will be collected through patient discharge. Endpoints will be clinical outcome and adverse events, including death, intracranial hemorrhage (ICH), stroke and major bleeding events. The final study protocol will be submitted to FDA by August 31, 2000, enrollment started by September 30, 2000, enrollment completed by June 30, 2002, and a final study report submitted to FDA by December 31, 2002.
2. Institute a specification for _____ in the _____ used as a raw material for _____ of TNKase™ by June, 2001.
3. Institute action limits on bioburden for all stages of the manufacturing process by June, 2001. Submit to CBER in-process bioburden data obtained from the next TNKase™ manufacturing campaign (to be conducted summer, 2000).
4. Develop a quantitative release assay for the fraction of TNKase™ which has been _____ by June, 2001. _____ to estimate the percent of product containing the _____ will be used with an action limit of _____ until the validated release assay has been established.
5. Collect data on the _____ TNKase™ in the bulk drug substance manufactured in the next two TNKase™ campaigns to assess if the _____ is supported by the results. Revise the _____ for _____ TNKase™ if appropriate.

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6. Perform studies designed to confirm the recovery/detection efficiency of the _____ assay in the presence of _____. The results of these studies will be submitted to CBER by December 15, 2000.

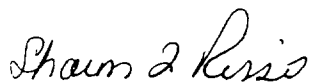
We note that ongoing clinical trials involve use of lower doses of this product in combination therapy. Please be aware that such combination use may necessitate future changes to your product labeling. If combination therapy is approved, it is our expectation that Genentech, Inc. will work with the Agency in making timely modifications to labeling, and potentially product packaging, to ensure safe and effective use of your product.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, MD 20852-1448.

Please submit final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



for Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research